SAFETY, TOLERABILITY AND EFFICACY OF SUBLINGUAL ALLERGOID IMMUNOTHERAPY WITH A 4-DAY SHORTENED BUILD-UP PHASE

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SUMMARY

■ **Background:** Sublingual specific immunotherapy (SLIT) with monomeric allergoid has shown to be safe and effective in all the studies performed so far. The build-up phase, however, is rather time consuming mainly if performed with the conventional schedule of 14 weeks.

■ **Aims of study:** We evaluated the possibility of shortening and simplifying this phase, through a new build-up scheme of only 4 days, as well as the persistence of the allergoid SLIT efficacy after 12 months.

■ **Methods:** Thirty-nine patients (26 M, 13 F, mean age 20.5 years, range 6-49) with a history of moderate/severe rhinitis with or without mild asthma due to perennial and/or seasonal allergens entered the study. The posological schedule, adopting only 1,000 AU tablets, was the following: 1/2 tablet the 1st day; 1/2 table twice the second day; 1/2 table plus 1 table the 3rd day; 1 tablet twice the 4th day; 1 tablet twice weekly from the 5th to the 365th day (maintenance therapy).

■ **Results:** Only two mild adverse reactions occurred during the initial phase which disappeared with the prosecution of the treatment. During the maintenance therapy no adverse event was observed. Symptoms improved consistently and drug consumption was reduced in most of the patients.

■ **Conclusions:** The 4-day shortened build-up phase resulted to be safe, well tolerated and effective, already after one year of treatment.

Key-words: Asthma - Build-up phase - Sublingual immunotherapy - Rhinitis.

INTRODUCTION

Specific sublingual immunotherapy (SLIT) with monomeric allergoid has been shown to be clinically effective and well tolerated in many clinical studies (1-5). However, the induction build-up phase is rather troublesome and time-consuming, requiring from a maximum of 14 weeks (traditional schedule) to a minimum of 16 days (semi-rush schedule). In fact the build-up phase of SLIT has been designed according to the same criteria used for injective immunotherapy, where side effects are frequent, local and systemic, in some (rare) cases serious and even life-threatening. The safety profile of SLIT showed to be much higher compared to injective immunotherapy, and systemic and anaphylactic reactions are virtually absent, as documented by clinical trials and post-marketing surveillance studies (6).

Aim of present study was to evaluate the possibility of simplifying the initial build-up phase of SLIT with monomeric allergoid by shortening the induction phase to 4 days, keeping under strict monitoring the safety and tolerability. The maintenance treatment has been prolonged for 1 year, and clinical efficacy evaluated at the end of the period.

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MATERIALS AND METHODS

The study was open and observational, without a control group, and the patients' management was in according to the current protocols of medical practice in force in the hospital. Inclusion criteria were: moderate/severe allergic rhinitis, with or without moderate asthma, due to perennial or seasonal allergens, positive prick test, positive CAP ≥ class 2. Exclusion criteria were in accordance with the summary of the product characteristics. All the patients expressed their informed consent.

Thirty-nine patients (26 males, 13 females, mean age 20.59±10.34 years, range 6-49) have been enrolled in the study, affected from rhinitis alone (n. 14) and rhinitis+ asthma (n. 25), monosensitized to the following allergens: house-dust mite (n. 27), grass pollen (n. 7), olive pollen (n. 3), cat dander (n. 1) and Parietaria pollen (n. 1).

Immunotherapy treatment sets consisted of monomeric allergoids, obtained by the manufacturer with

carbamylation (K cyanate) at neutral pH in order to substantially decrease the allergenic potency by substitution of Â-amino groups of lysine (7), titrated in biological units (AU) and incorporated into orosoluble tablets (LAIS®, Lofarma, Milan, Italy). In present study just the maintenance treatment sets were used (1,000 AU oromucosal tablets) and following the schedule described in Table 1. As recommended in the patient's leaflet, the tablets were kept in the mouth for 1-2 minutes before swallowing. The duration of the treatment was 1 year. All the patients were instructed to take for symptom control the following medications: cetirizine tablets (10 mg, once daily), inhaled albuterol (100 μg, 2-4 puff on demand), intranasal fluticasone (50 μg, 1 spray per nostril once daily on medical prescription. In the case of severe rhinitis unresponsive to the standard treatment, a short course of systemic steroid was given prednisone 50 mg daily for 3 days). To evaluate efficacy have been used a visual analogic scale (VAS) before and after the treatment, and a mean cumulative score related to the reduction of symptomatic medications.

RESULTS

All the patients tolerated very well both the induction build-up phase and the 1-year maintenance treatment. During the build-up phase just two slight side effects have been recorded, one case of somnolence and one of tiredness, both no more observed in the continuation of treatment. No side effects have been registered during the maintenance treatment.

As regards efficacy, in all the patients a constant improvement of the VAS scores was observed. The mean score was 2.97 at baseline and 6.28 at the end of the study. Moreover it was possible to observe a significant decrease of the drug consumption both for mites ($p<0.001$) and pollens ($p<0.01$). From a clinical point of view the greater reduction was observed in pollens-treated patients.

Day	Number of table
1° day	1/2 tablet (in presence of the allergologist)*
2° day	1/2 tablet (in the morning) + 1/2 tablet (in the evening)
3° day	1/2 tablet (in the morning) + 1 tablet (in the evening)
4° day	1 tablet (in the morning) + 1 tablet (in the evening)
5°-365° day	1 tablet twice weekly (maintenance therapy)

Table 1: Four-day build-up schedule with monomeric allergoid in orosoluble tablets.
*The patient was kept under observation for at least 20 minutes.

DISCUSSION

The schedule used for the induction build-up phase in present study has two peculiarities, the shortness of the up-dosing, 4 days, and the fact that the beginning dose was quite high, half tablet containing 500 AU, corresponding to the half of maintenance dose. That allows the handling of a unique type of tablet titrated at 1,000 AU, then simplifying consistently the treatment and preventing mistakes in dosages. Besides, with the present schedule the maintenance phase can begin early, with consistent advantages both as regards the adherence to the treatment and the quickness in reaching clinical benefits. The schedule employed in present study consists in administering a cumulative dose of 5,000 AU in 4 days, slightly higher than that (4,000 AU) employed by Rossi & Monasterolo in their ultra-rush up-dosing study, where the administration of all the dosages lasted only 20 minutes (9). In both the studies the administration of such high dosages in a short time did not determine the appearance of relevant adverse reactions: one case of oral itching out of 45 patients (2.2%) in the Rossi & Monasterolo study, two cases (5.1%) of somnolence and tiredness in present study. In both the studies no side effects have been observed during the maintenance phase. Similar results were obtained in the study of Gammeri et al. (9) where the ultra-rush (20 minutes) SLIT build-up phase with monomeric allergoid provoked just one case of gastric pyrosis out of 105 treated patients, 26% of which were children. On the whole, these data confirm the optimal tolerability and safety of the SLIT monomeric allergoid already demonstrated by Lombardi et al in an observational survey on 198 patients treated for 3 years with this product (2). On the other side, in a study performed on 100 children aged 3.5-17 years following an ultra-rush up-dosing schedule of 40 minutes, with commercial extracts from two companies containing native (not chemically midified to allergoids) allergens, Tripodi et al (10) observed during the up-dosing phase light adverse reactions in 8.7% of patients with one extract and in 41.9% of patients with the second extract, declared by the manufacturer at high dosage. The very low frequency of side effects observed in present and other studies employing allergoids is probably ascribable to the low IgE-binding activity of the active principle. Even if present study, being open and observational and without a control group, was unfit to allow a correct evaluation of efficacy, nevertheless the observed favourable modification of VASs and the reduction of symptomatic drugs consumption suggest satisfactory clinical results, after just 12 months of treatment.

In conclusion, SLIT allergoids administered according to a shortened 4-days build-up phase, starting directly from 500 AU (corresponding to half of the mainte-

nance dose), is safe, well tolerated and effective. The minimal side effects observed disappeared with the prosecution of treatment. The efficacy was evident already after one year of maintenance treatment.

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